



# Increased COX-1 Expression in Benign Prostate Epithelial Cells is Triggered by Mitochondrial Dysfunction



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## Introduction

### Abstract

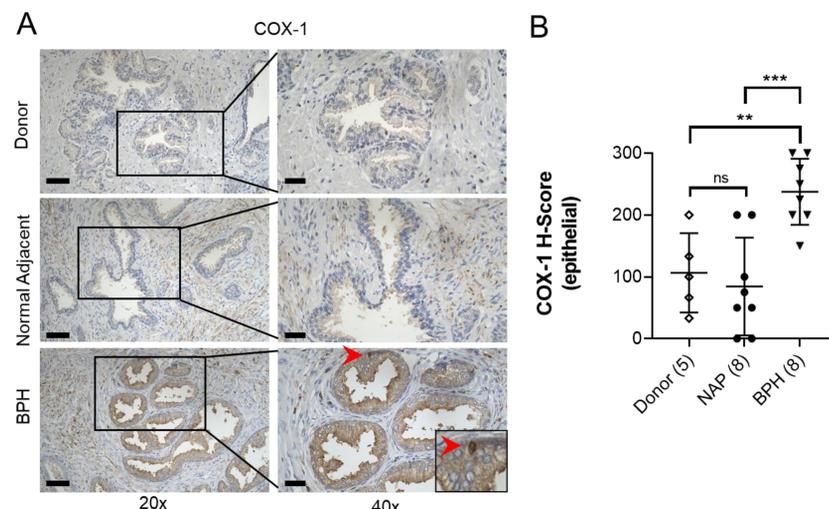
**Introduction and Objectives:** Benign prostatic hyperplasia (BPH) is an age-related disease associated with chronic prostatic inflammation. Aging is associated with decreases in mitochondrial functional capacity. Increasing metabolic stress may contribute to the release of pro inflammatory mediators potentially contributing to BPH progression or mediation. Cyclooxygenase-1 (COX-1) and cyclooxygenase- 2 (COX-2) are enzymes responsible for converting arachidonic acid to proinflammatory mediators (i.e. prostaglandins and thromboxanes) and are well-established drug targets. Prior studies focused on COX-2 selective blockade with lackluster improvement in BPH symptoms. We recently reported that stromal COX-2 immunostaining was increased with age but not altered in BPH tissues, and epithelial COX-2 had no differences in expression with age variation or BPH tissue type. However, it is unknown whether COX-1 is differentially expressed in response to age or tissue type. Here we looked at COX-1 expression in human tissue and potential pathways that could be involved in regulation of COX-1 and COX-2 within prostate cell lines.

**Methods:** The expression of COX-1 was analyzed in 22 clinical BPH specimens by multiplex immunohistochemistry and in two murine models of BPH and lower urinary tract dysfunction. Human prostate epithelial cell line RWPE-1 was treated with TGF- $\beta$ 1 and rotenone (complex I inhibitor) to determine the impact of inflammatory cytokines and mitochondrial dysfunction on COX-1 and COX-2. RWPE-1 cells were transfected with small interfering RNA specific to complex 1 gene NDUFS3.

**Results:** COX-1 expression was increased in the epithelial cells of BPH specimens compared to young healthy organ donor and in mouse models of BPH and lower urinary tract dysfunction. Cell line assays showed that mitochondrial complex 1 inhibition via rotenone or NDUFS3 knockdown induced an up-regulation of COX-1 and COX-2.

**Conclusion:** Our findings suggest COX-1 can be induced in benign prostate epithelial cells in response to mitochondrial complex I inhibition and is elevated in BPH epithelium. COX-1 may play more of a role than previously recognized in the development of age-related benign prostatic disease.

## COX-1 immunostaining is increased in BPH epithelial cells



## Conclusions:

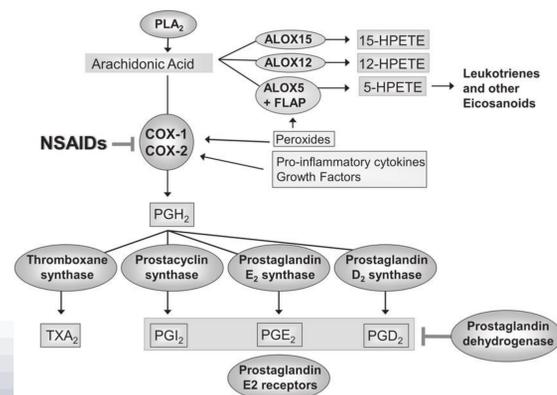
COX-1 expression is increased in BPH  
 Disruptions in mitochondrial function triggers increased expression of COX-1 protein in prostate epithelial cells  
 BPH epithelium is characterized by altered mitochondrial function

## Inhibition of mitochondrial complex 1 increases Cox-1 and Cox-2 expression in benign prostate epithelial cell line RWPE-1

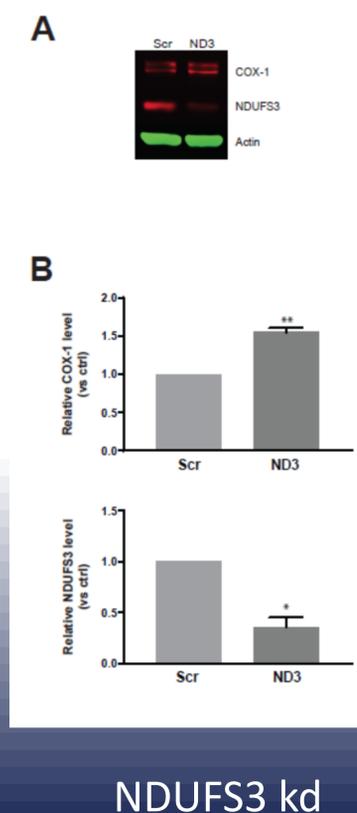
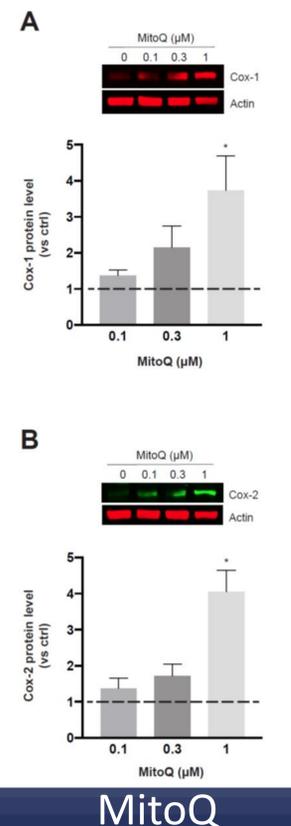
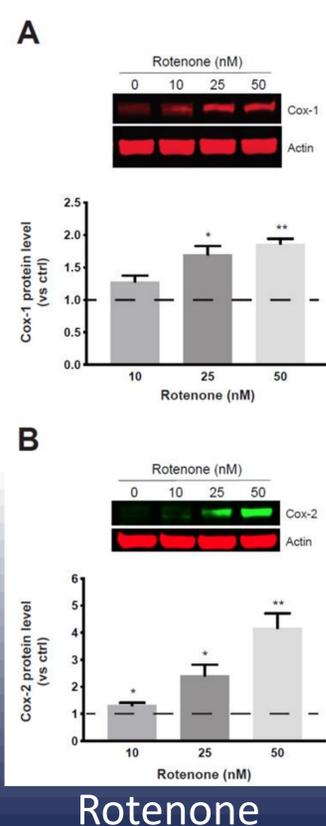
## Possible Implications

### Dual Activation of the Inflammatory Cascade

COX-1, expressed in most cells, is traditionally associated with housekeeping functions like maintaining gastric epithelial cytoprotection and regulating homeostasis while COX-2 is induced by inflammation and is thought of as the more prolific source of prostanoid formation. However, both COX-1 and COX-2 contribute to prostanoid release during inflammation. [3]



Resler, Alexa J., et al. "Genetic variation in prostaglandin synthesis and related pathways, NSAID use and colorectal cancer risk in the Colon Cancer Family Registry." *Carcinogenesis* 35.9 (2014): 2121-2126.



Our results suggest a COX not typically associated with an inflammatory state (i.e., COX-1) may be an important contributor to the production of pro-inflammatory mediators in the aging prostate.

The differential impact of COX-1 and COX-2 on the signaling mediators derived from arachidonic acid metabolism has not been thoroughly investigated in many organ systems but given our results, could provide insights into age-related changes in prostate tissue homeostasis.

Our results in a prostate epithelial cell line suggest that mitochondrial dysfunction associated with aging may be partly responsible for altering the balance of arachidonic acid metabolites driving tissue homeostasis through selective effects of COX-1.